Ankara Med J, 2018;(2):198-206
DOI: 1017098/amj.435258

Metabolic Syndrome in Rheumatoid Arthritis and Ankylosing Spondylitis

Romatoid Artrit ve Ankilozan Spondilitli Hastalarda Metabolik Sendrom

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Abstract
Objectives: To evaluate and compare the prevalence of insulin resistance and metabolic syndrome (MetS) in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and to determine the relationship of MetS with disease-activities and the factors associated with MetS.
Materials and Methods: The cross-sectional study included a total of 174 patients with RA and AS. MetS was defined according to the International Diabetes Federation (IDF) criteria. Insulin resistance was assessed with the Homeostasis Model Assessment (HOMA) Index. The Disease Activity Score including 28 joints (DAS28) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were used to measure disease activity. Functional status was evaluated using the Health Assessment Questionnaire (HAQ) and the Bath Ankylosing Spondylitis Functional Index (BASFI). Logistic regression analysis was applied to identify predictors of metabolic syndrome.
Results: The prevalence of MetS was significantly higher in patients with RA (47%) than in patients with AS (24.56%) (p=0.005). The prevalence of insulin resistance was significantly higher in patients with RA (34.18%) than in patients with AS (17.54%)(p=0.031). No significance difference was found in the disease activity score between RA and AS patients with metabolic syndrome and without metabolic syndrome (p=0.580 and p=0.158, respectively). The number of patients with a higher BASDAI score was greater in AS patients with MetS. Age and body mass index were determined to be predictors for MetS (p=0.015 and p<0.001, respectively).
Conclusion: Higher rates of MetS and insulin resistance were seen in RA patients compared to the patients with AS. Better control of the MetS components and disease activity may help to decrease the prevalence of MetS in rheumatic disease.
Key words: Metabolic syndrome, rheumatoid arthritis, ankylosing spondylitis, disease activity

Öz
Amaç: Romatoid artrit (RA) ve ankilozan spondilitli (AS) hastalarda insülin direnci ve metabolik sendrom (MetS) prevalansını değerlendirmek ve karşılaştırmak, MetS'in hastalık aktivitesi ile ilişkisini ve MetS ile ilişkili faktörleri belirlemektir.
Materyal ve Metot: Kesitsel çalışma toplam 174 RA ve AS'li hasta içermektedir. MetS Uluslarası Diabet Federasyonu Kriterlerine (IDF) göre tanımlandı. İnsülin direnci Homeostas Model Assesment Index (HOMA) ile değerlendirildi. Hastalık aktivitesini ölçmek için 28 eklemi içeren hastalık aktivite skoru (DAS 28) ve Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI) kullanıldı. Fonksiyonel durumu Bath ankilozan spondilit fonksiyonel indeksi (BASFI) ve sağlık değerlendirme ölçeği (HAQ) kullanılarak değerlendirildi. MetS belirleyicilerini tanımlamak için çoklu regresyon analizi kullanıldı.
Bulgular: MetS prevalansı RA'lı hastalarda (%47) AS'li (%24.56) hastalardan daha yüksekti (p=0.005). İnsülin direnci prevalansı RA'lı hastalarda (%34.18) AS'li (%17.54) hastalardan daha yüksekti (p=0.031). MetS olan ve olmayan RA ve AS'li hastalar arasında hastalık aktivite skorları arasında anlamlı fark bulunmadı. (sırasıyla p=0,580 ve p=0,158,). Yüksek BASDAI skorlarına sahip hasta sayısı MetS'li AS hastalarında daha yüksekti. Yaş ve vücut kitle indeksinin MetS için belirleyici olduğu saptandı (sırasıyla p=0,015 ve p<0,001).
Sonuç: AS'li hastalarla karşılaştırıldığında RA'lı hastalarda MetS ve insülin direnci yüksek oranda görüldü. MetS komponentlerinin ve hastalık aktivitesinin daha iyi kontrolü romatolojik hastalarda MetS prevalansının azalmasına yardımcı olabilir.
Anahtar kelimeler: Metabolik sendrom, romatoid artrit, ankilozan spondilit, hastalık aktivitesi

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Date of submission: 30.01.2018
Date of admission: 24.05.2018

Introduction

Rheumatoid arthritis (RA) and Ankylosing Spondylitis (AS) are chronic, systemic, inflammatory disorders of unknown etiology that are associated with increased disability, morbidity and mortality. As these patients are prone to increased risk of cardiovascular disease and the associated complications, cardiovascular disease is one of the most common causes of death in this patient group.[1] However, the traditional cardiovascular risk factors, including smoking, hypertension, dyslipidemia, insulin resistance and diabetes mellitus do not fully explain the excessive cardiovascular risk in rheumatic diseases. In recent years, evidence has indicated that metabolic syndrome (MetS) may provide an important link between increased cardiovascular risk and inflammation in these diseases.[2]

Metabolic syndrome (MetS) is a cluster of specific cardiovascular (CV) disease risk factors including central obesity, hypertension, insulin resistance and dyslipidemia. The number of people with MetS is increasing worldwide, closely related to the increasing rates of obesity and insulin resistance. Moreover, although the exact underlying mechanism is not known, the prevalence of MetS and insulin resistance is higher in those with rheumatic diseases than in control populations.[3]

The aims of this study were, i) to determine the prevalence of MetS and insulin resistance in patients with RA and AS according to IDF criteria; ii) to compare the prevalence of MetS in patients with RA and AS; iii) to evaluate the relationship of MetS with disease-activity, and iv) to identify the risk factors associated with metabolic syndrome.

Materials and Methods

Patients

This cross-sectional study included a total of 174 patients (RA=117, AS=57) and was conducted in the Department of Physical Medicine and Rehabilitation, Dışkapı Yıldırım Beyazıt Training and Research Hospital. Patients were included who met the 2010 ACR/EULAR classification criteria[4] for RA, or the New York criteria for the diagnosis of AS[5] and were aged ≥18 years. The exclusion criteria were patients with any other autoimmune or inflammatory disease and those who refused to participate in this study.

The study protocol was approved by the Local Research Ethics Committee. The study adhered to the guidelines of the Declaration of Helsinki and informed consent was provided by all participants.

Clinical Assessment and Laboratory Tests

Basic demographic data including age, gender, education level, marital status and clinical data related to the diseases, including disease duration, rheumatoid factor, and cyclic citrullinated peptide (anti-CCP) were recorded for each participant. Body weight, body height and waist circumference were measured. The waist circumference was measured midway between the lower rib margin and the iliac crest. Blood pressure (BP) was measured with a mercury sphygmomanometer in the sitting position after five minutes of rest. The laboratory data including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting glucose, high-density lipoprotein (HDL) cholesterol, and triglycerides were also assessed. Insulin resistance (IR) was assessed with the Homeostasis Model Assessment (HOMA) Index. HOMA index = (insulin (μIU/mL) x glucose (mgr/dL))/405. If the HOMA index was ≥2.5, it was defined as insulin resistance.

A record was made for each patient of the drugs used (systemic corticosteroids, DMARD, biological agents) and the disease activity according to the Disease Activity Score including 28 joints (DAS28) for the RA patients and disease activity according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for the AS patients. A DAS28 score of 2.6-3.2 indicates low disease activity, >3.2-≤5.1 moderate and >5.1 high disease activity. A Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of >4 indicates high disease activity.

Functional status was evaluated using the Health Assessment Questionnaire (HAQ) and the Bath Ankylosing Spondylitis Functional Index (BASFI). The reliability and validity of the Turkish version of the HAQ was tested by Kucukdeveci et al [6] and the reliability and validity of the Turkish versions of the BASDAI and BASFI have been previously shown.[7,8]

Metabolic Syndrome Definition

One of the most widely used definitions for MetS is the International Diabetes Federation (IDF) criteria, according to which it is the presence of central obesity (Waist circumference ≥94 cm in males or ≥80 cm in females), plus at least two of the following items: 1) Serum triglyceride (TG) levels ≥150 mg/dl, or those who are undergoing drug therapy; 2) high density lipoprotein (HDL) cholesterol <40 mg/dl in males or <50 mg/dl in females; 3) systolic blood pressure (SBP) 130 mm Hg; diastolic systolic blood pressure (DBP) 85 mmHg or patients treated for hypertension; 4) fasting blood sugar (FBS) 100 mg/dl or previously diagnosed type 2 diabetes.[9]

Statistical analysis

Data obtained in the study were analysed using SPSS for Mac, Version 20.0 software (SPSS, Chicago, IL, USA). Data were presented as mean ± standard deviation for continuous variables and as number (n) and percentage (%) for categorical variables. The Chi-square test was applied for comparison of proportions. The Student's t test was used to compare the mean values of continuous variables between the groups. If the distribution of the continuous variables was not normal, the Mann-Whitney test was used for comparison. Multiple logistic regression analysis was conducted to identify the predictors for MetS. Univariate analysis was applied first between each predictor and the presence of MetS to identify the variables that were included in the multivariate model. Those variables with p<0.20 in univariate analysis and identified individually as a significant predictor were entered into the multivariate model. The

stepwise method was used to compare the influence of different factors and types of factors on the presence of MetS. The level of statistical significance was set at $p<0.05$.

Results

Evaluation was made of a total of 174 patients comprising 131 (75.28%) females and 43 (24.71%) males with a mean age of 51.26±12.67 years and mean BMI of 29.69±5,98 kg/cm^2. The underlying diagnoses of the participants were RA (n=117) and AS (n=57).

The mean disease duration was 7.42±6.76 years in the RA group and 6.38±7.14 years in the AS group. Female predominance was observed in both groups. In comparison with the RA patients, the AS patients were significantly younger ($p<0.001$). BMI, fasting glucose and systolic blood pressure values were higher in the RA group than in the AS group ($p=0.016$, $p=0.033$, $p=0.001$, respectively). Using the IDF definition, the prevalence of MetS was significantly higher ($p=0.05$) in RA patients (n=55, 47%) than in AS patients (n=14, 24.60%). The prevalence of insulin resistance was significantly higher ($p=0.031$) in RA patients (n=40, 34.20%) than in AS patients (n=10, 17.50%). Statistically significant differences were determined between the groups in respect of the level of HOMA-IR ($p=0.044$). All the demographic and clinical characteristics of the patients are presented in Table 1.

When the demographic and clinical characteristics of the RA and AS patients with and without MetS were compared (according to IDF), age and BMI showed a statistically significant difference in RA and AS patients with MetS ($p=0.020$, $p=0.09$; $p=0.001$, $p=0.001$ respectively). No significance difference was determined between AS and RA patients with or without MetS in respect of disease activity score. The number of patients with a higher BASDAI score was higher in the AS patients with MetS and the patients with MetS had a higher BASFI score (Table 2).

Multivariate logistic regression analysis was performed to examine the variables associated with MetS in patients with RA and AS. Table 3 shows the results of the logistic regression model for the OR of MetS in patients with RA and AS for age, gender, BMI, presence of RA versus AS and erythrocyte sedimentation rate. A significant correlation was determined in both groups between MetS and age and BMI (OR, 1.04; 95% CI, 1.00-1.07 and OR 1.14; 95% CI, 1.06-1.22). MetS was not seen to be associated with gender, presence of RA versus AS or erythrocyte sedimentation rate.

Discussion

MetS is a common problem, which in recent years has been considered to be a major contributory factor to mortality and morbidity in rheumatic disease. This study investigated the frequency of MetS and insulin resistance, the factors associated with MetS and a comparison was made of the prevalence of MetS in patients with RA and AS. The findings revealed that 47% of the RA patients and 24.6% of the AS patients had MetS according to the definition of the IDF criteria. The prevalence of MetS was significantly higher in the RA patients than in the AS patients. In addition, the results of the multivariate analysis showed that MetS was associated with age and a high BMI value.

Table 1. Characteristics of RA and AS patients

	RA(n=117)	**AS (n=57)**	***p***
Age (years)*	55.62±11.46	42.33±10.17	**<0.001**
Gender			**<0.001**
Female	99 (84.61%)	32 (56.14%)	
Male	18 (15.38%)	25 (43.85%)	
BMI (kg/cm²)*	30.45±6.15	28.13±5.33	**0.016**
Disease duration (year)*	7.42±6.76	6.38±7.14	0.355
Disease activation			
DAS 28	3.30±1.37		
BASDAI		2.40±2.31	
Higher disease activation (DAS 28 >5.1, BASDAI>4)	12(10.2%)	12(21.0%)	
Waist circumference (cm)*	98.92±13.63	94.46±15.64	0.057
Systolic blood pressure (mm/Hg)*	128.16±18.89	115.70±15.01	**<0.001**
Diastolic blood pressure (mm/Hg)*	77.82±11.95	75.0±9.06	0.086
Laboratory Data*			
Glucose (mg/dl)	95.50±29.05	87.61±18.81	**0.033**
TG (mg/dl)	145.85±75.58	128.13±63.54	0.131
HDL(mg/dl)	51.83±13.80	50.19±16.56	0.494
Sedimentation (mm/s)	25.0±16.89	20.0±14.04	0.055
CRP (mg/L 0-8,normal range)	10.02±13.18	10.20±11.52	0.932
HOMA-IR	2.70±3,21	1,76±1.93	**0.044**
Prevalence of insulin resistance	40 (34.18%)	10 (17.54%)	**0.031**
Prevalence of MetS	55 (47.0%)	14 (24.56%)	**0.005**

*Mean ± standard deviation. RA rheumatoid arthritis; AS ankylosing Spondilitis; MetS metabolic syndrome; BMI body mass index; DAS28 28-joint disease activity score; BASDAI Bath Ankylosing Spondylitis Disease Activity Index; TG triglyceride; HDL high-density lipoprotein, LDL low-density lipoprotein; CRP C-reactive protein; HOMA-IR Homeostasis Model Assessment –insulin resistance.

Table 2. Comparison of risk factors, patients' characteristics and laboratory measurement for Metabolic Syndrome.

	RA (n=117) MetS		***p***	**AS (n=57) MetS**		***p***
	(+)	(–)		(+)	(–)	
n	55 (47%)	62 (53%)		14 (24.6%)	43 (75.4%)	
Age (years)*	58.22±10.39	53.31±11.94	**0.020**	48.41±10.03	40.32±9.54	**0.09**
Gender			0.803			0.227
Female	46 (83.6%)	53 (85.5%)		10 (71.4%)	22 (51.2%)	
Male	9 (16.4%)	9 (14.5%)		4 (28.6%)	21 (48.8%)	
BMI (kg/m²)	32.39±6.24	28.72±5.58	**0.001**	32.82±5.34	26.63±4.42	**<0.001**
Disease duration	6.51±5.93	8.31±7.35	0.153	7.67±6.81	5.91±7.23	0.444
Disease activity						
DAS 28	3.37±1.18	3.23±1.52	0.580			
BASDAI				3.32±2.86	2.10±2.05	0.158
HAQ	0.56±0.68	0.61±0.75	0.741			
BASFI				2.74±2.63	1.01±1.61	**0.034**
The patients with high disease activity score (DAS 28 >5.1, BASDAI>4)	5 (9.09%)	7 (11.29%)	0.767	7 (50.00%)	5 (11.62%)	**0.005**
Laboratory Test*						
Sedimentation (mm/s)	25.42±15.21	24.63±18.36	0.802	25.14±17.60	18.33±12.46	0.115
CRP (mg/dl 0-8, normal range)	9.91±11.68	10.1±14.4	0.927	8.1±4.8	10.86±12.96	0.455

*Mean ± standard deviation. RA rheumatoid arthritis; AS ankylosing Spondilitis; BMI body mass index; DAS28 28-joint disease activity score; BASDAI Bath Ankylosing Spondylitis Disease Activity Index; HAQ Health Assessment Questionnaire; BASFI Bath Ankylosing Spondylitis Functional Index; CRP C-reactive protein.

The prevalence of MetS has been seen to vary in different studies according to the definition criteria used, sociodemographic variables such as age, education, and income, and disease severity and duration that contribute to insulin resistance, impaired glucose tolerance, dyslipidemia and increased atherosclerosis in rheumatic disease. The current study showed that 47% of the patients with RA had MetS. Similar to the present study, Karvounaris et al[10] conducted a study of 200 patients with RA to evaluate MetS and reported the prevalence of MetS among the patients to be 44%. In contrast to that and the current study, Özmen et al[11] and Mok et al[12] reported MetS prevalence of 28.8% and 20% in patients with RA. A difference fact was observed.

However, in those studies, there was observed to be a much lower proportion of patients with diabetes mellitus and hypertension and a higher proportion of younger patients which could explain the lower rates of MetS. In addition, patients with AS have been reported to have a higher prevalence of MetS than healthy control groups. MetS prevalence was observed to be 45.8% by Malesci et al[13], and 10.5% by Batmaz et al in patients with AS.[14] In the present study, MetS prevalence was found to be 24.6% in patients with AS. Furthermore, the patients with RA had a significantly higher prevalence of MetS compared to the AS patients. This could be attributed to RA patients having more comorbidities including MetS components such as diabetes mellitus, hypertension, and hypertriglyceridemia. Similarly, in a study by Dabrowski et al[15] comparing MetS in AS and RA patients, higher rates of MetS prevalence were determined in RA patients compared to AS patients.

Table 3. Multivariate logistic regression analysis with MetS as dependent variable

	OR	95% CI	*p*
Age	1.04	1.00-1.07	**0.015**
Gender (female)	1.03	0.43-2.42	0.47
BMI	1.14	1.06-1.22	**<0.001**
RA (against AS)	1.38	0.57-3.36	0.466
Sedimentation	0.99	0.97-1.02	0.938

OR, Odds ratio; CI, Confidence Interval; BMI; body mass index; RA rheumatoid arthritis; AS ankylosing spondilitis.

Insulin resistance plays a key role in the underlying mechanism of metabolic syndrome that has been linked to low-grade inflammation and obesity. Abdominal obesity is the major indicator of insulin resistance in the general population.[16] Insulin resistance is a frequently observed problem in rheumatic disease. The current study showed that the RA patients had a significantly higher prevalence of insulin resistance, indicating that those patients were at greater risk of MetS than the AS patients. The results of the current study were consistent with the findings of Dabrowski et al. Therefore, insulin resistance should be evaluated for the prevention of MetS in rheumatic disease.

The interaction between functional status, disease activity and MetS in patients with rheumatic disease is complex and controversial. An increase in proinflammatory cytokines as a result of chronic inflammation alters insulin receptor activity which contributes to the development of MetS. However, unlike most previous studies[10,17,18] the current study findings did not reveal a significant relationship between disease activity and the presence of MetS in either group. Nevertheless, AS patients with a higher disease activity score also had a higher prevalence of MetS, so, it can be considered that MetS is closely related to a chronic inflammatory state which can affect the disease activity in AS patients.

BMI and increased age were found to be risk factors for MetS in both the RA and AS groups. Increased age may result in increased frequency of comorbidities including MetS components.[19] Similar to the the present study, De Oliveira et al[20] showed that age was an independent predictor of MetS in patients with RA. Obesity is known to have a major role in the development of MetS. It has been suggested that obesity is associated with chronic inflammatory responses characterized by abnormal cytokine production and activation of inflammatory signaling pathways.[21,22] The current study results showed that obesity is a predictive factor of MetS in patients with AS and RA.

The present study has some limitations. The major limitation of the study was that it did not have a prospective controlled design. The cross-sectional design did not allow the causality of the associations to be examined. Second, inflammation status changes frequently in rheumatic disease, so inflammation markers and disease activity score may not represent the long-term cumulative inflammatory burden. Third, the sample size was small in this study, so further studies with greater number of patients may allow the investigation of more factors associated with MetS.

In conclusion, the present study showed that the RA patients had higher rates of MetS and insulin resistance than the AS patients. Advanced age and a high BMI value increase the risk of the development of MetS in patients with AS and RA. For the management of MetS in rheumatic disease, there should be better control of the metabolic syndrome component and disease activity, and excessive weight gain should be prevented.

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